Scolnick, Edward 1998

Dr. Edward Scolnick Oral History 1998

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National Cancer Institute Oral History Project

Interview with Edward Scolnick, M.D.

conducted on June 24, 1998, by Gretchen A. Case

at Dr. Scolnick's office at Merck Laboratories in West Point, Pennsylvania

GC: Let's start with how you came to the NIH since you worked at the Heart Institute before you worked at NCI.

ES: Okay. I ended up at NIH and in the Heart Institute in the following way. I had done some research in college and a little bit in medical school. The work was reasonably unsuccessful, and it had actually convinced me that research was not the place for me to be.

So I was in medical school trying to figure out what I would do after I graduated and was an intern, and realized in something like my junior year in medical school that there was a war on in Vietnam and I didn't want to go there as a draftee. So I started looking into options for how to avoid doing that.

Among the things that I learned about was going to NIH in the Public Health Service and doing research. So, since I still liked research, even though I didn't think I could be very good at it based on my experience, I explored that option. Ended up getting an application to the Heart Institute, which was the place recommended to me by various professors, and wrote and applied. Got recommendations, and went through an interview process for being accepted to the Institute. I was accepted. This was . . . I think when I was an intern, I can't quite remember.

And then the process was to . . . about a year before you were due to come, which was after the first year of residency in medicine, you were invited to come and visit with all the lab chiefs in the Heart Institute to put together a matching list of who you wanted to go to and how you rank them and how they rank candidates coming, and you would end up in a lab a year later when you came there. So I went down to visit with all the people in the Heart Institute at the time. There were some interesting labs.

The one lab that had caught my fancy before the last interview was with a biochemist named Roy Vagelos who was in Earl Stadtman's lab at the time with his own section and I liked what he was doing, I liked him, and I told him, "Gee, I think I might like to come here." He told me not to apply because he was probably going to leave NIH to become Chairman of Biochemistry at Washington University in St. Louis, and I'd end up without a place to go. So we had a nice conversation and that was kind of left the way it was.

Then later, toward the end of my visit, that day or two, I visited Marshall [W.] Nirenberg and sat down and talked to him. I knew who he was, I knew what was going on in the lab, I'd always been interested in genetics, at least in what I had done in college and medical school, and I had a really terrific conversation with him for a couple hours. He explained to me what they were doing in his laboratory, what was going on, had a long philosophical discussion about being a scientist and being in a competitive field, and I decided after the conversation that this was the place to go. That even if I wasn't successful in research, it would really be an exciting couple of years, he was a unique person, and I'd learn a lot and have a good time, and then I'd go on my way and do something else.

So I came there in July '67, and when I arrived, Marshall said, "Well, my lab's changing now over the last year. I'm going to spend all my time now doing research on neurobiology, and the system I've picked is" something, there was a worm and he showed me all these worms in his lab in his tanks, and a small group in the lab's still continuing to work on the genetic code. There was a person named [C. Thomas] Tom Caskey who headed that up at that time, and gave me a choice of working in neurobiology or with him directly or working with Caskey in his lab environment. I didn't want to work in neurobiology. I thought it was premature for me to do something like that, and I ended up working in the genetic code for two years.

That was fortuitous, positive circumstance, the project was really interesting, we were working on the last part of the genetic code at the time trying to figure it out and the biochemistry of it. And after a year of pretty much getting nowhere in the project based on an assay that Tom Caskey dreamed up, we had an inroad into the problem and then for a couple of months the research went really spectacularly well. We made some absolutely novel discoveries, creative discoveries, the most important of which occurred sometime in the late summer of '68 which really changed my life completely in research. All the materials and technical assays for asking a set of critical questions about the biochemistry of this problem, protein chain termination, were available.

Tom went on vacation, it was myself, another research associate at the time, Tom's technician named Theresa Caryk, and we were setting out to purify a factor responsible for chain termination based on this assay from e-coli. We started the process of preparing material and purifying it and we all had a different assay to run because we were tracking two or three different factors at that point. Late one day late in the week of that week, we got a wonderful peak of activity for this termination factor off of one of our biochemistry columns. I was responsible for some of those assays and Theresa was responsible for some of them, and she brought me the plot of the activity late one afternoon—it was very late in the day—and it was really terrific. We had found this termination factor.

It was clear, and this thing kind of came off of the column that we were fractionating it on in a clear peak that went up and started down, and it was about three-quarters of the way down when she had finished that number of fractions from the column. And I said to her, "Theresa, we should really finish defining the peak before we leave because we don't know how labile this activity will be, so why don't you run another ten tubes out, you know, run every other tube and take it out of another twenty or thirty tubes and make sure we get it down to baseline, we'll pool the peak, we'll freeze it away and we'll be all set. We'll be ready to go and do experiments."

So she did that and came back, and I ran my part of those assays and she came back with the plot off the scintillation counter about an hour later, it was pretty late, it's maybe six, six-thirty at this point, and the peak started to come down, it went down, and there was a second peak. It came up and started down. And that was completely unexpected, a really surprising result, and in looking at it I said, "Well, we can't go home now!" There were three triplets involved, three codons involved in termination at that point and we were assaying for one of them.

I said, "Take the peak tube from this one and the peak tube from that one and run them against each of the three triplets, and I'll finish just the simple assays." So she did that and came back again maybe another hour later and lo and behold, this [first] peak recognized two of the three triplets and this [second] peak recognized two of the three triplets. One of them was in common and the other two were different, and we knew then we had a really terrific discovery, that we had really cracked the mechanism of chain termination and that we had the factors that recognized triplets and they were proteins, not transfer RNA's which is what recognizes the rest of the genetic code. And that was in my research life at that point the most exciting thing that had ever happened to me. We were sure it was right.

Tom was on vacation. I called up Marshall at home—he was at home, this was pretty late, maybe eight o'clock at night—and told him what we had found. His first question was prototypic of Marshall. He said, "Are you sure it's reproducible?" [Laughs] And I said, "It's reproducible. You can tell from the data." I went over to his house and showed him the data. He was just as excited as we were. We finished up pretty late and went home, and I realized at that point that I could never not do research. The excitement, the *high* involved with that discovery was so great that it was like being addicted to something, and I knew that I just had to stay in research at that point. Marshall and Tom had taught me why I had never been successful before. They taught me a process of doing research that really changed my ability to get reproducible results and carry out experiments, and then this event really changed everything. So over the next year, year-and-a-half we really took apart the mechanisms of protein chain termination and published a number of really important papers that were widely recognized.

I wasn't sure what I wanted to do in the long run because it was clear most of the work then in the genetic code was done, but I knew I wanted to stay in research. A lot of people at the time were sort of in the same boat who had been in bacterial genetics and were talking about working in animal virology instead of bacterial virology, and so I learned about a Cold Spring Harbor course on animal virology, asked Marshall if they would send me to the course in the summer of '69, and everybody thought that was a great idea.

And I went to Cold Spring Harbor in the summer of '69 and for six weeks—I think it was six weeks, maybe a month, I can't remember . . . maybe two weeks—a period of a few weeks and took a lecture and lab course on animal virology. The course was very well taught by a distinguished senior virologist who used to be a professor at the University of Connecticut—I can't remember his name—and the people in the course were really a fantastic group of people. They were much more senior in science than I was, and they were all there for kind of the same reason, to learn about animal virology. People like Ann Skalka, Phil [Philip] Leder, Maxine Schwartz, who is now head of the Pasteur Institute—he was quite a bit younger at that time—and some other folks like that. It was a great couple of weeks, learned a lot, was very excited.

Came back to the Heart Institute and realized that even though I had been offered a position there to stay in that lab, that Marshall really was dedicated to doing worm work, didn't have the resources to set up somebody to do animal virology, so I really had to find somewhere else to do that. So while continuing to work on the things we were working on there, I started looking around for where I would go. I looked in universities, and then I learned about the kind of stuff that was going on in the Cancer Institute in tumor virology, and I learned about [Robert] Huebner and George Todaro who were collaborating at that point in tumor virology.

And I went and interviewed with Todaro who had, at that point, a better molecular reputation. He had a lab that NCI had set up as a contract operation but was really an in-house lab in Virginia, in Springfield, Virginia, in a company called Meloy [sp?] Laboratories. Their facilities were great, the projects were interesting, the people I met seemed okay, and so I elected to give up my permanent position at NIH for a staff associate's job in Cancer [NCI] with the promise that it could be turned into a permanent position, and started commuting every day to Virginia from Wheaton, Maryland, which is where we were living at the time. It's not fun, in a small, used Austin American I had bought which always broke down on the beltway.

But in any case, it was a very exciting time. In the months before going down there, I started reading about the systems they were working on and realized that the conceptual framework for understanding so-called RNA tumor viruses was missing, how they replicated was not clear, there was a real conundrum based on the work that Howard Temin had done, and Hidesaburo Honafusa and other people like that and was trying to figure it all out. Went to a lecture in early June in downtown Washington that Sol Spiegelman gave in which he claimed he had found the enzyme that replicated RNA tumor viruses and he claimed that it was an RNA-dependent RNA polymerase. I realized, as I was listening to the lecture, that didn't make any sense because there was a role for DNA in their replication and it didn't explain that.

And basically arrived a few days after that to work in Meloy Labs, and after about a week there, one morning George Todaro wandered into the office I shared with two other people, Stu Aaronson and Wade Parks, and said, "David Baltimore just called me. He'd like a large amount of purified Rauscher's leukemia virus, which was an RNA virus, RNA tumor virus, because he's just found an enzyme in Rous sarcoma virus that he thinks is the secret to the puzzle about how they replicate." He and Temin had just discovered an RNA-dependent DNA polymerase which was revolutionary at the time.

And that was a great discovery because it really opened up the field conceptually, and it gave us tools—conceptual framework and tools for working with the viruses.

When I heard about that, I said to myself, "That explains how they replicate. It still doesn't explain how they transform cells and cause cancer." Shortly after that, David Baltimore visited our lab and we were introduced to him and just talked about the field, and we set out to do what we could to take advantage of this observation. The main goal of Todaro's lab was to find a human RNA tumor virus. So most of these projects were focused on that, and the technologies we were developing were focused on trying to detect that, and I spent the first year of my time down there working on this enzyme, using it as a tool to look for human leukemia viruses and it was a productive time because there was so much new to be discovered based on the Temin and Baltimore discovery.

By the end of a year or so, it was clear that there wasn't an easy, quick way to find RNA tumor viruses using this enzyme, that there was a lot more basic understanding that was needed, and I began to think about what else to do in the field. I was always interested in the cancer part, not the replication part, and began to work on understanding the genetic structure of one of these prototype RNA tumor viruses. And the virus chosen was chosen purely by chance. It was the virus being worked on in that lab, it was called the Kirsten sarcoma virus.

It had been discovered a long time before by a University of Chicago-based virologist called Werner Kirsten. There was a virus he had worked with called the Kirsten leukemia virus, and there was a virus called the Kirsten sarcoma virus. Had different biologic properties and I was trying to figure out what the genetic differences were.

The only methods available at that time were molecular hybridization, this was before DNA cloning could be done, and the techniques weren't there. So there were, in retrospect, primitive hybridization methods available but we were utilizing them and I set the techniques up in the Todaro lab, culling different things from the literature and we started comparing the structure of leukemia and sarcoma virus by these methods.

Toward the second year of my time there while this work was getting off the ground, Wally Rowe and Janet Hartley, Doug Lowy, and Natalie Teich [sp?] in their lab discovered that you can induce latent occult RNA tumor viruses from B-alb C-3T3 cells, a low leukemia incidence mouse using the BUDR [sp?]. And published that. Their work was transmitted in a luncheon meeting to us at Meloy Labs in Virginia because they came down and asked for cell lines, Todaro, Aaronson, myself, and others, and it was decided after that lunch by Todaro and Aaronson that they really wanted to work on following up that observation with Rowe and Hartley because they were still interested in finding a human leukemia virus. I did not want to follow that course of research, and therefore began an attempt to have my own lab set up somewhere else at NCI, and Huebner was terrific in this regard because Wade Parks and myself, who were colleagues, both wanted to do something else.

Huebner worked out a way to set us up in a lab in Rockville, in Meloy in Rockville, another building they owned, contract money was made available, the facility was renovated, it was an old cow barn, it was a lab that had taken care of cows and sheep, we needed a really complete renovation so nice renovations were done. They weren't fancy but they were clean. We had tissue culture hoods installed, incubators, and labs were set up to do biochemistry. We took the projects we were working on and moved up there and started a laboratory from scratch. We worked together, Wade and I, for the next seven or eight years—whatever it was, five or six years—until he got divorced and moved away from the area.

So I continued to pursue in the first year of the move the genetic analysis of the sarcoma leukemia virus. For about six months had very striking differences by molecular hybridization that were really quite interesting. I showed there were major genetic differences between the viruses. Some of it made conceptual sense.

The sarcoma virus was found to lack major portions of the leukemia virus genome, and that made sense because it could not replicate. Sarcoma virus had other information in it that was not in the leukemia virus, and the techniques at the time didn't allow you to do anything with that. You couldn't just clone the gene, sequence it, and start unraveling what the oncogene was. There was no technology to do that. So we were kind of stuck. We had this data, and it was interesting, but we had no conceptual framework for it. So we didn't quite know what to do with it while other projects in the lab were ongoing.

One Sunday morning—I lived in Rockville not far from the lab—one Sunday morning I had been told about a history book on tumor virology written by Ludwik Gross, he was one of the fathers of tumor virology. One Sunday morning I was reading the Ludwik Gross book and I noticed there was a chapter in the book about Werner Kirsten. I opened the book to the chapter on Werner Kirsten and—I was actually in the bathroom reading the chapter—and I got to a certain part of the chapter and it said, "Dr. Kirsten took the Kirsten leukemia virus in order to keep it so that it caused leukemia in animals, he had to passage it many times in mice and periodically pass it in mice, couldn't carry it in cell culture. And then one day he took the virus and he passed it in rats. And after a passage or two in rats, put it back into mice and it caused a different kind of tumor. It caused a sarcoma and a erythroleukemia, and then after subsequent rat passage it caused it even faster and now the virus actually transformed fibroblasts in cell culture."

And when I read that, I said, "Oh my God. This material that we found that's in the sarcoma virus that's not in the leukemia virus came from the rat."

I lived five minutes from the lab. I went immediately up to the laboratory and opened up the notebooks with the data and looked at the data to see if it made sense conceptually with what I had thought. And it made perfect sense. Absolutely perfect sense. I was a hundred percent convinced that the sarcoma virus had rat genetic information in it, and so I said, "How am I going to prove this?" I thought about it for about an hour and I figured out how we would conceptualize the experiments, and then went home. The next day we started a series of experiments to try to prove the theory that the virus had picked up its information from rats.

Technically in those days, which were '72, '73, again before genetic cloning, it was very hard to make good DNA copies of the RNA viruses. It was not hard to make copies, it was hard to make *good* copies. Technology was evolving all the time, Spiegelman's lab was heavily involved in trying to improve the technology, and we did the right conceptual experiment many times and we couldn't get a good answer. Couldn't get a clean answer because the probes we were making were not good enough. They weren't clean enough. The backgrounds and the assays were always too high, and it was very frustrating. And then we read a paper out of Spiegelman's lab on how to purify the DNA probes, so we set up to make a whole new series of purified DNA probes. This was in '73. We hadn't done anything terrific at that point. This project was still not fruition, and I had an offer at that time to go to the University of Texas Medical School-Southwestern to become a tenured professor of virology and join their Department of Medicine in microbiology. It was a really terrific school, I knew some people there, and I had gone down once and I went down for a second visit to go over details of the offer because I thought it was worth doing. We were in a contract lab and things were not stable, et cetera.

So on the weekend before going down, I got all the materials ready for my technician and wrote up the protocols, took a copy of the protocol with me to Texas, went through the days of interviews. Pretty much told them at the end of the day, "I think I want to come. I just want to think it over."

I went back to the airport, and when I was in the airport I called the lab and I asked my technician whose name is Elaine Rands [sp?], "Hey Elaine, what happened in the experiment?" And she said, "Well, I don't know. Some things hybridized and some things didn't." And I said, "Oh? In the past, everything hybridized because the backgrounds were too high. Read me the counts. I have the protocol with me." And she read me the protocol. It was a perfect experiment. Perfect experiment. A hundred percent clear cut that the material came from rats. A hundred percent clear cut. I told her, "Elaine, it's perfect. Here's the interpretation of the experiment. It's absolutely perfect." That was my second déja vu in science since the termination stuff. I got on the plane and I said, "No way I'm leaving to go to Dallas because this is a great project now. We're just going to pursue this for the next five years." And I did. I called them back and said, "Sorry, not coming." I couldn't really explain why because I couldn't tell anyone about our data yet. Then we finished up the experiments and wrote up a paper for the *Journal of Virology*, which was published in 1973, and I gave a talk at a Gordon [Research] Conference that summer, which everybody really appreciated, on the findings. And then over the next five years we worked on that system very hard and slowly unraveled the secrets of that system which turned out to be the *ras* system. And then as molecular cloning became available, we could really perfect the studies in the late '70s and early '80s to really completely define the genes and the proteins.

In the late '70s, after the protein or Rous sarcoma virus had been found, there was a much better system than ours. We were trying to find the protein coded for by this stuff that was the oncogene, or what we thought were related to the oncogenes, and we had no tool, we had no handle, it was not a tyrosine kinase, and we decided to do what had worked for our sarcoma virus. Transplant rats, transform cells or membranes from them and immunize various animals and look at sera and set up a way to look for the protein by radiolabeling and precipitation.

That went on for the better part of a year with absolutely futile results. The people in the lab doing the actual work, a couple technicians and a post-doc, came to me one day and they said, "We don't want to do this anymore. This project's going nowhere, we're sick of it, we're tired of getting negative results, we will not do any more experiments." I said, "Okay. There's one more set of sera to screen. It's probably not going to work. We have some tumors from rats transplanted with these transformed cells from the rat's gene." And we thought that was the least likely place to find an antibody because it was a rat-derived virus transplanted as a tumor back into the rat. I said, "Why don't you just finish up all the sera including the rat sera and we'll just give up for a while."

Then one day a few days later, I passed one of the techs in the hall and I said, "How did the last study come out?" And she said, "Well, it's different. Something lit up on the gels but it's the wrong molecular weight based on the size of the rat insert that we knew was in the virus." I said, "Oh? Let me look at the gels."

So I went and looked at the autoradiographs and again it was a perfect experiment. It was absolutely specific for the *ras* transformed cells. So it was clearly an oncogene protein. But it was the wrong—it was a small molecular weight protein. It was twenty-one thousand [inaudible]. I said, "I don't care what size it is. Maybe it's being broken down. That's the real McCoy. Look at all the controls." So we repeated experiments, we worked through whether it was a degraded precursor, we did a lot of biochemistry. We clearly had it, unambiguously had it and we had an assay for it and lots of anti-sera and it came from rats. Unbelievable.

So we made buckets of this stuff by transplanting more tumors, described it, wrote it up, and then started to try to figure out what it did.

In my early days in Virginia with Todaro I had labored to make a mutant of the Kirsten sarcoma virus which was temperature sensitive for transformation. I got one good mutant and its properties, like all-temperature sensitive mutants, were that it transformed cells at a low temperature, thirty-two degrees, thirty-three degrees, and at thirty-nine degrees the cells reverted to normal. You shift them back and they became transformed. That was always a genetic marker for a thermal labile protein. Temperature-sensitive protein.

So after laboring around—and we noticed in the course of our immuno-precipitation experiments that the protein from the temperature-sensitive virus lost the ability to be immune-precipitated with our sera if we heated the extracts up, the radiolabeled extracts before we immune-precipitated. So we knew the protein was in fact the protein because it correlated to the genetic temperature sensitivity of the virus. But we didn't know what it did.

And one weekend, again just sort of thinking about how to approach the problem, I came in and I said, "We're going to try a classic biochemistry experiment. We're going to take every co-factor known for every enzyme known to man and we're going to go through methods and enzymology, we're going to line them all up, we're going to pre-incubate them with these temperature-sensitive extracts, heat them up, and then try to immune-precipitate them. We're going to look for something that will stabilize the thermal ability of the protein hoping that it's a co-factor for the enzyme that will help us figure out what the enzyme does.

So we lined up everything under the sun we could think of. Twenty different things that we had in the lab, and we did the experiment. And lo and behold, big black band that we could immune-precipitate—everything else was gone—was with two things, GTP and GDP. Nothing else worked that we did. It was an absolutely crystal clear experiment. I said to the technician whose name was Patricia, "Pat, you must have mixed it up. This must be ATP." She said, "No, I did not mix it up. It's GDP and GTP. We can repeat the experiment."

She repeated the experiment and it worked again, perfectly. So we had a GTP binding protein which at the time was absolutely novel in tumor virology. And we immediately thought about what it might do and how it might work based on that. We did all our controls, we did the experiments, and a couple days later I went over to Wally Rowe's lab—he was in the National Academy of Sciences and we had been friends—and I said, "I've got something I really want to show you. Will you sponsor this for the NAS?" And he looked at it and he said, "That's terrific. You really have cracked the problem." I said, "I'll get it to you through the next deadline" which was a couple weeks later so we furiously wrote all this up, got everything ready, gave it to him, he got it reviewed, made some modifications, and we published it. Then we set out to further try to unravel the biochemistry. We did a lot of that over the next few years.

Two kinds of directions happened in the lab. We did a lot of biochemistry on it and more genetics, cloning became available to really define the system well, and a lot of really elegant analytical work was done. Along the way we decided we wanted to work on a real leukemia virus at the time so we had a post-doc in the lab named David Troxler, who was from Duke, who was really a smart, terrific young man, and we decided we wanted to work on Friend virus because it was a rapid leukemia in mice. It caused an erythroleukemia in mice. F-r-i-e-n-d, discovered by a woman named Charlotte Friend who was in Mount Sinai in New York. Done all the original descriptive biology.

The virology of that system was a mess. It was not at all clear what was going on, and we decided however—and this was the beauty of being at NIH, and I would emphasize this. You could pick up a project like this without having it go to any funding agency and you could just start working on it and we did that.

We spent about a year learning the system and fiddling around with the system and asking some basic questions so we just understood the basics of the system. If we had had to do this to go through a grant committee, we could never have done this project. Absolutely never done the project.

At the end of a year, we had a very good conceptual framework for what was going on, but we didn't have a technical handle on it. Again, this was pre-molecular cloning. And we dreamed up an absolutely insane way to biologically clone this virus in fibroblasts, not hemopoietic cells, because you couldn't culture hemopoietic cells to clone it, and the virus didn't transform fibroblasts so you couldn't recognize the fibroblasts morphologically with the virus in it . . . even though the virus was replicating it because if you shot it back into mice it caused a fulminate erythroleukemia.

So we dreamed up this wild scheme, which was very labor-intensive but very cute, and we were very careful about how we did it. We geared up a lot of people all at once because it was a very labor-intensive project. We got through the first phase and we decided we were going to get a non-producer cell containing the replication defective of fulminate leukemia virus and clone it that way and then we would rescue it with helper. That way we would have the fulminant virus in the absence of helper and then we'd be able to analyze it molecularly even though we couldn't see the fibroblasts.

We worked out a biologic cloning technique to do that, a very large experiment. We had very good resources. We grew up at least a hundred individual clones done blindly, froze them all away. The first thing we did was grew them up, freeze them away so we saved them and pulled them out small amounts at a time, added helper, let it grow for a while, fired it into mice.

Bingo. Fifth clone. Zap. We had it. Did it again. It was there again.

We analyzed it biologically and we had isolated the fulminate erythroleukemia virus in a morphologically unchanged fibroblast. Every time we added helper we'd pull out the rapid virus and fire it into animals.

We wrote this up and published it and started working on it molecularly. Wrote it up and published it. All the people in the Friend virus field thought we were crazy. They thought we had been insane. This is impossible. It can't be done. This virus doesn't grow in fibroblasts, it can't be isolated in fibroblasts, you guy have created an artifact. There's just no way. There is the data. The real molecular virologists in the field understood what we had done. The historical people in the Friend virus field just about ostracized us.

Meanwhile we went over for the next year molecularly doing the same kind of hybridization studies we'd done with Kirsten virus to uncover the oncogene as with this erythroleukemia virus. We came up with an astounding result that it was an envelope protein, recombinant envelope protein between two different mouse leukemia viruses, not a classical oncogene, based on hybridization studies. We were so flabbergasted by this that—and it was very surprising that we . . . meanwhile we always tried to make antibodies again in the same way we'd done it.

We repeated this experiment over and over in many different ways for about a year before we published it, because we knew no one would believe it. But at that point we were a hundred percent sure, we had other evidence from immunology that we were doing on the side, it was starting to work that we were right, so we wrote it up and published it. And poor David got up and presented this at a Cold Spring Harbor meeting with tremendous consternation from, again, the historical people in the field, and then they went back to their labs and over the next year they tried to repeat the experiment. They couldn't do it.

Every time David would go to a meeting, they'd say, "It's an artifact. You guys screwed up, you're wrong, you really set the field back ten years, this is all bullshit. All an artifact." So he said, "No it's not. It's a hard experiment to do, we've done it many different ways," and then about a few months later we started publishing and talking about the immunology data which confirmed it and then everybody realized we were right and they finally started being able to confirm the experiment.

That experience drove David Troxler back to medicine. It was one of the things that made him decide to leave research. It was too bad because he is a terrific scientist. There were other reasons he decided to go back to medicine, too, but it was a very unfortunate circumstance.

Then molecular cloning came along and we cloned that virus and we cloned Kirsten and Harvey virus, which was like Kirsten, and for two or three years there was really the most—I mean you couldn't pick up an experiment on any day where you didn't discover something fantastic about the structure of these viruses and what they were doing because the cloning was so powerful. We proved unambiguously that this protein was the oncogene for Friend and we did a lot of elegant stuff on Harvey and Kirsten.

And then I decided that at that point I didn't want to keep doing this for the rest of my life. The field was someday going to connect to human cancer—I was sure of that. So were a lot of people in the field. That wasn't a novel observation, and I started looking around for what to do with myself.

I took a sabbatical in England to learn about bone marrow hematology related to leukemia virus, did that for about six months, came back, continued to work in the lab, things were going well. I was not feeling as creative and I knew I didn't want to just keep doing this kind of research.

Along the way, there was one incident that had come up which had been an amusing incident, which I'll come back to in the middle of all this.

[End Side A, Tape 1]

[Begin Side B, Tape 1]

GC: OK.

ES: Along the way, we had had another really interesting incident which was a highlight or a low-light of my life at NIH. And that is that as the various oncoproteins were being described and a little bit about them was being discovered in the early days of the '80s, it wasn't clear how they fit together biochemically in a pathway and that was really the key question then in the field, and that's where I felt I just wasn't being very creative. I didn't know really how to go about doing that. And then one day a rumor emanated from Cornell from Efraim Racker's lab. A young guy named Mark Spector [sp?]—

[Interruption in tape]

—but I'll never give up the originals.

GC: Okay.

ES: And a rumor emanated from Cornell that a young man in Ephraim Racker's lab—Ephraim Racker is a great historical biochemist, did some brilliant work in biochemistry—had discovered a link between the tyrosine kinase oncogenes and *ras* and that there was a kinase in cells that phosphorylated *ras, ras* was a substrate for tyrosine kinase and really cracked the problem open. So, I called up Mark Spector and talked to him and said, "Gee, this is really exciting. Tell me something about it and would you like to work with us on the project. We've got all these cells and genetic things and maybe you can help me figure it out."

So he said, "Well, explain what you've got, explain your system," and I explained to him the *ras* system and the kinds of cells we had and what we could give him that would help him figure out what he really had. And he said, "Terrific. Send me the cells." So I said, "Great. I'll send you the cells, see if it works, and if it does, we'll have you come down and give a seminar and we can figure out how to work together." So we sent them up a bunch of cell lines and a couple weeks later he calls me back and says, "The experiments worked. We've got it." It's the enzyme that phosphorylates.

It phosphorylates the *ras* protein and he sends me back a gel, and these are the control cells, and these are the *ras* transformed cells, and these extra bands here, the heavy band and the band above it, these here are what he's making. He's phosphorylating the *ras* protein in those cells. This is a picture of an autoradiogram. [Scolnick shows Case the radiogram as he talks.] And one of it is the allegedly methionine labeled, this is methionine labeled, and these are the same bands P32 labeled from his phosphorylated. Enzyme is phosphorylating the *ras* proteins. A perfect experiment if you match up the lines. The bands correspond perfectly.

And I say to him, "Gee, Mark, that's really terrific. You sent me this and now you've really got it—we've been looking for this enzyme since you told us about it and we just can't find it. Would you mind coming down and giving us a little, so we can work in the field? We'll credit you." And he said, "Give me about a month and I'll come down." I said, "Terrific. Wonderful."

So we arranged for him to come down, we knew when he was coming on a Monday morning from New York in the wintertime. The weather held up long enough, he came, we had everything ready in the lab. I had my best technician, a woman who had worked for me for years, Jean Mariak [sp?], work with him in the morning. We had all the extracts ready and he had his tubes and they worked together and they went through a protocol and put the things in the counter before lunch. Bing! Everything worked. And we lined up the counts with the protocol.

So we went off to eat lunch. I said, "Jean, how about repeating the experiment over lunch while we're eating? Do you mind?" She said, "No." She goes and takes the things out of the tubes, does the same thing, she was terrific. We came back after lunch, she goes to the counter, nothing worked. Nothing worked.

So we scratched our heads and Mark's there and we said, "How come it didn't work?" He said, "Well, it's very tricky. It's a very labile enzyme." So we tried again and it didn't work. So this time it's getting late and everybody's tired and a little frustrated, so we put everything away in the freezers. He was going to stay overnight and we were going to work on it again the next morning and the arrangement had been to stay at my house in Rockville.

So I brought him home to dinner, had dinner with my family, and dinner conversation. After dinner I went in the living room with him while things were getting cleaned up and I talked to him. "Something's wrong. I can't figure out what's wrong." And I kind of was more and more interrogating him. Anyway, after the dinner goes on, he says, "I'm going to take a walk."

So as he goes to take a walk, my wife comes out of the kitchen and comes in and says, "What are you attacking that young man for that way?" I said, "Barbara, there's something wrong here. I can't put my finger on it. There's something wrong. It doesn't add up." And she said, "You're just being paranoid and you're competitive with this young guy. Just leave him alone."

So anyway, he comes back. We have casual conversation and he goes to sleep—we had a finished attic, a nice room where he was to sleep. And we go to bed and wake up in the morning and I go down to start coffee, which is my wont, and he's not downstairs. So anyway it's getting late so I go up to the attic and the door's open. So I knock on the door, there's no answer. I go upstairs and look for him in the room and he's not there, and more than that, the bed's not slept in. So I said, "This is crazy. This is absolutely crazy. What is going on?"

He was out taking a walk, he comes back, and he says—he eats breakfast—and he says, "I really got to go back to Cornell. The weather's going to be bad today. I'll leave you this [enzyme]—I'll go back to your lab." I said, "Okay, and we'll get you a cab and go to the airport." And he goes back and I'm talking to somebody and he leaves to go to the airport, and then we look in the freezer where all these things were supposed to have been left and there's nothing there. So we're just absolutely mystified.

Anyway, we said, "Okay. If he can find this enzyme, we can find this enzyme." So we started a big project in the lab to make extracts of cells and look for the enzyme in phosphorylates, the *ras* protein, tyrosine kinase. And we spend six months, intense frustration, every way we know how, all the tricks I'd ever learned in biochemistry, and we can't find the damn thing. And meanwhile, a couple of times I ran into Racker at meetings and I'd say, "Dr. Racker, you're a great biochemist and I am just a schlepper in biochemistry, and we can't find this enzyme. Would you please tell us what's wrong?" He said, "Well you guys, it's just very sophisticated. It's just too hard to do and only a few people can do it, and I'm the best—" traditionally he's a Krebs type biochemist, Fritz Lipmann [sp?], you know, the best biochemist in the world. And I say, "Oh, it must be. We're just not good enough."

Then we give up. After six months we give up, we can't get anybody back to the lab to help us, and we just give up. Meanwhile, there's a big—in the field people saying, "Is it real? Is it not real?"

One day I get a phone call from Racker's assistant professor, whose name I can't remember, he's in the department, and he says, "Ed, do you still have the vials from when Mark was in the lab?" I said, "Yes. We've never thrown out anything because we've given up." He said, "Put them in the scintillation counter and check the spectrum of the counts." So we do it, and we—I said, "I'll call you back in a few minutes."

So we do what's necessary to check the spectrum, and lo and behold, it's not P32, it's iodine. He was dry-labing the experiments. He was iodinating the proteins in vitro with chlorine T. It was a complete artifact—it was worse than an artifact. It was deliberate fraud. Deliberate fraud. And I said, "It's all iodine." He said, "Yes, that's what we found here, too." And he said, "We're going to have to go public with this. It's all complete fraud."

So it was written up in *Science*, and I have saved these autoradiograms. I will never throw—they'll go in my grave with me, because again we were just—Racker just ridiculed—every time I talked to him he just ridiculed us about how we couldn't do this kind of biochemistry. This is Spector's- writing on this stuff. I thought someday it might be good for an archives somewhere.

Anyway, toward the early '80s, at that point I decided I didn't want to keep doing this kind of basic research and I didn't know what I wanted to do and I started to look around. I said, "Someday this will be connected to human cancer, and what am I going to do when that happens? I can keep doing what I'm doing, it's going to be a lot of diagnostic stuff. What cancers have what oncogenes, mutated or changed and related to the cancers, and then there'll be new therapies hopefully. Anti-things against the proteins or the genes." I said, "I'd like to do that. I wonder if I can do that here?" So I started with—there were only a few chemists around NIH at that point, so I went and talked to people and I realized how little I knew, and I said, "Boy, it's going to be pretty tough to do here. I don't know what to do. I think I'll just keep doing what I was doing."

One day out of the blue I got a phone call from a recruiter from Merck saying, "Merck's looking for somebody to come in and start a molecular virology group under Morris Hilleman"—who is a great traditional virologist who made mumps, measles, rubella vaccine—"are you interested?" I said, "Well, now why don't you come talk to me? Maybe." I had looked at a job in New York that I had decided not to take. And [they] came down and met with me and I said, "I'd like to look at it." And the other reason I wanted to look at it is the head of the labs at that point was a man named Roy Vagelos who I had met twenty years ago at NIH, and he had been so open with me about the fact that he was going to leave and he didn't want me to make a mistake in who I applied to that I said, "Well, if I'm going to go to a company instead of an academic institution, that would be a good guy to be around."

So I went and over the course of the next year or so through a very--that's not related to NIH--a lot of convoluted discussions with Merck, I ended up deciding to go to Merck and I accepted their job offer in February of '82. About six weeks later, Bob Weinberg calls me up and he says, "We have a gene that we have found in a human bladder carcinoma cell line that we can transfect into another cell and it is an oncogene from a human cancer, and we have reason to believe it might be the *ras* gene. You have the clones, will you give us the clones to test it out?" I said, "Absolutely we'll give you the clones, the anti-sera, anything you want." Shipped everything up there. It turned out to be *ras*. And we had the same cell in the lab actually. We knew, had confirmed in our own labs, that it was the *ras* oncogene. The paper was published in *Nature* and it was the first demonstration of a mutated human oncogene in a human cancer. At that point I had mixed feelings because the field had broken open very, very widely, and on the other hand I said, "Gee, it's really true." So I go to Merck, I'm going to try to make an anti-*ras* drug. We knew a little bit about the biochemistry at that point.

So I came here and my career here is not for this tape, but we started to work on how we would try to make an anti-*ras* drug. For five years we—while we were here, shortly after we were here, because the group I brought with me, some of the people I brought with me were clearly, were the only molecularly trained people in the lab. They were involved also with a Merck project on hepatitis-B made in yeast, and we had some yeast DNA around, and one of the technicians, who was much more than a technician, named Debbie Jones, decided to look for RAS in yeast, a gene related to RAS in yeast. And she found a band. It lit up. She showed it to me and I said, "Boy, that's great. Clone it out and see if it's really RAS," because that would really open up the pathway. She cloned it out, sequenced it, it was *ras*. Bona fide *ras*. And we published that.

We were the first ones to publish that in *Nature* in 1983. Cold Spring Harbor laboratory jumped all over that observation. We couldn't really work on the basic things here as well as we otherwise would have because it was not really a Merck project. We did a lot of work, collaborated with, a geneticist at Penn, a yeast geneticist named Kelly Tatchell, and we did a lot of really nice stuff that got the essence of the system out.

Cold Spring Harbor did much more because they had a big focused effort on it. And over the next two or three years, *ras* and yeast and its biochemistry became unraveled, it further opened up the field, and a few years later, while we were laboring and getting nowhere on our approach to the *ras* drug, a geneticist in yeast from the West Coast—again I'm awful on names, I'm blocking his name---called me up and told me he had found an enzyme in yeast that prenylatd *ras* and it might be a target for blocking *ras* activity because for other reasons, we knew that that step was important for getting *ras* to the active state from an inactive precursor that we had discovered years ago.

So we decided we would go after that here, and we did and the group changed immediately what we were doing and we went after making an inhibitor of that enzyme called the farnesyl transfer enzyme, and we started working on it, a lot of people did including the people on the West Coast and people in Dallas, Joe Goldstein and Mike Brown. The biochemistry of the enzymes became clearer over a couple of years and we labored hard for five or six years to make an ideal inhibitor of that enzyme, which we had shown along the way if you block it, *ras* will not transform, it's not that toxic, it had fantastic results in onco-mice that carry an activated Harvey *ras* oncogene, and probably twenty pharmaceutical companies in the world are now working on trying to make a farnesyl transferase inhibitor as a potential cancer drug. Two others have compounds in the clinic now, we have a compound in the clinic with proprietary knowledge that we've discovered about the system at this point and confident we have the only one of the three that we know about today that has a chance to work, it's the best one so far that anyone's come up with, and we've learned something that gives us an edge in the field.

We have wonderful animal data. It's truly spectacular, and we are in phase one of clinical trials with this drug which blocks the lipidation of all *ras* proteins and has fantastic results in animals and synergizes with other chemotherapeutic regimens in animals done by us and done by people outside of here in collaboration.

So my career has come full swing from the beginning of the problem in 1972 to having an inhibitor of the protein, the activity of the protein, in people and it will be tested as an anti-cancer drug in two or three different kinds of regimens over the next twelve to eighteen months.

So it's a very exciting time for me. On the one hand I have absolute faith, based on all the data I've seen in animals, that this is going to work. On the other hand, we don't have a shred of evidence in people that anything's happening yet. It's too early in the way you do these trials to see activity yet, but there is simply no evidence in people that it's going to work yet. But we'll know over the next year, year-and-a-half, whether the concept is correct or not and whether one can really make an antagonist inhibitor of one of these oncoproteins and do something with clinical cancer taking a completely rational, traditional pharmaceutical company approach to discovering a drug but a completely non-traditional approach to discovering a cancer drug. It's trying to put the rational basis into cancer drug discovery which is why I wanted to come here in the first place. At which point that's the last thing I want to do here. That's a private conversation. The archives can have it because by the time people here [at Merck] know it, I will have told them that.

But it's a good feeling because if it doesn't work it doesn't work, but I think it'll work and I think it'll change the cancer therapy field because a lot of companies are trying this kind of approach on other proteins, and once one works in people well, everyone will take this general approach. My prediction is there'll be a whole new—over the next ten or twenty years there'll be a variety of new kinds of anti-cancer drugs based on the science that NCI funded in the war on cancer program twenty years ago. It's not a waste of money. Many people have said that was a waste of money. It was not a waste of money. It opened up the cancer field, it allowed people to identify and define the HIV virus, which is a human retrovirus, much faster and to do something about it much faster than had that work never gone on. And even though it was a lot of money, and it seemed like waste, it was not wasted at all. It'll be interesting to see how it all plays out over the next year or two.

GC: That was actually one of my questions for you because I knew there was a lot of criticism of the war on cancer and especially of the SVCP, the Special Virus Cancer Program. I'm just wondering how that impacted you because you were working on it.

ES: A lot of the criticism was justified. On the other hand, if you look in the totality of things in a perspective, the amount of money that was spent is very small compared to how much is spent on bombers and bombs and planes. And even though there might have been some waste, a lot of that money found its way into really quite meaningful basic science programs in AIDS research that helped unravel the AIDS project and has now dramatically changed the cancer field forever. There were operational administrative issues that were not good in that program, but Huebner, who was the father of that program, really did something good for the world in creating that program.

How it impacted on me, I was always the bastard child of that program. I didn't want to work on finding a human virus, and we were constantly working on this oddball system called the *ras* sarcoma virus which people looked at and said, "Gee, that's really fantastic basic research and it's not relevant to anything, but we'll humor this guy because he keeps doing these interesting experiments." And then when the Weinberg observation came up and it connected to human cancer, everybody said, "Gee, he was right. The foresight was there. This is terrific." By that time I had decided to leave, and they said, "Well are you sure you don't want to stay?" and I said, "No. It's time to do something else. You didn't appreciate me before the fact, I'll go off and do my own thing again [laughs] in another place where I think I can do what I want to do."

So that's basically the story of my life in NIH.

GC: Do you feel like that criticism was coming mainly from the medical and research field outside the NCI or—

ES: Of the SVCP?

GC: Yes.

ES: Oh yes. Some of both. A lot of it was outside because there was so much money in the SVCP that had not found its way into the traditional grant system that people were jealous of it and they wanted to get access to that money and they didn't feel they could get access to it. And they knew there was some waste, and there was some waste, but on the whole, it's trivial when you see the impact of the program twenty years later.

GC: What about in-house? Were people pretty supportive of the SVCP at NCI?

ES: Well, some were and some weren't. If you were in it and you were funded, you were moderately supportive of it because it was your support. If you were outside it and you couldn't get access to it and you saw some of the crummy science that some people were doing and some of the waste, you were very critical of it. So it was clearly a mixed program. But as I said, if you look back at it historically and the real impact—it's like a president and what their legacy really is, you can't tell for a while. It's the same concept. This program changed the world of cancer research and the AIDS research field. Dramatically changed those fields. So I don't think by any stretch of the imagination you couldn't say it wasn't a successful program.

GC: One of the criticisms of the program is that too few people had too much power.

ES: They did. Absolutely correct. Too few people had too much power. Absolutely correct. Huebner, John Moloney, Frank Rauscher, George Todaro had immense power. They controlled a five hundred million dollar budget probably—I don't know what the number was, but it's very high and that is true. The genius was Huebner. He had the vision, the genius of what to do, he was not mean-spirited, he could see the role for basic research as well as the targeted research, and he contracted with quality scientists. Not always traditional approaches, but quality people. That could not be said for some of the other people in charge of the program. But I think Huebner was a great man. A really great man.

GC: So are you generally supportive of the idea of contracting out parts of science? There's always been a controversy of grants versus contracts at the NIH.

ES: Right.

GC: Where do you fall in that whole controversy?

ES: I would rephrase it, Gretchen. What I used to feel when I was at NIH—I think the government's supporting basic research is vital for places like Merck to discover new therapies in any field. The Congress doesn't fund in a big way things that are not causes. If you look at the history of NIH funding you'll see that the big infusions of money into the NIH budget came with Sputnik, with the war on cancer, with the AIDS epidemic, and with the human genome sequencing project. In other cases, you putter along and you barely make it to keep up with inflation.

In order to get large amounts of funds into the biomedical community, and it has had tremendous benefit for people's health, you need a cause, and whether that cause comes through contract or through grants, funding targeted causes is not a bad thing, and the basic research community I think doesn't—some people appreciate that in the basic research community now. Not enough people appreciate that, and I don't think it matters whether they're contracts or grants. You need grants, you need investigator-initiated projects, you need some government-sponsored projects to get certain kinds of things done in different fields. But it's not either or. The key is to keep the funding up because it really has paid off for public health and people's health.

GC: How are we doing on time?

ES: Maybe a few more minutes.

GC: If you wouldn't mind just telling me what you feel—you can answer it one of two different ways. Either what was your favorite thing about working at the NCI or what do you feel was your greatest accomplishment or your biggest gift to the NCI?

ES: I think both. I'll answer both. The greatest feeling of positivity I had was in the discoveries that I described during this talk, I really think the great thing about the place was, and at NIH in general, was that you had unfettered time to devote to research, you had plenty of money to pursue your creative bents, however you wanted to do it, had lots of resources, you didn't have to go to anybody to ask them whether you could work on something. So I always felt that that was a great situation on the one hand, and the other hand that somebody who ran a group or ran a lab, as I eventually did, that you really had an obligation to work on projects that really could have an impact, a real impact. It gave you the opportunity to do that, you didn't need to do what in the grant system you need to do outside, which is churn out the papers every couple months whether the data was good or accurate or important, but whether it was biologically meaningful and important or whether it was just getting the papers out so you could maintain your grants. Never had to do that in NIH. That was a *wonderful* atmosphere for a young scientist to be able to pursue what they wanted to pursue. The obligation was that you shouldn't just turn out the papers. You really had to work on something that was truly meaningful. And we did that, and we did that over and over and over again and we had a big impact on the field.

The most exciting things were some of the discoveries I described to you. The discovery of the *ras* gene, the discovery of the protein, the biochemistry of the protein in the Friend virus. I mean those were fantastically exciting times. They were just great. Nothing beats that. The feelings were fantastic.

GC: When you say you were unfettered in terms of time, in terms of resources, in terms of people?

ES: Both. Both.

GC: Money was never?

ES: Money was never limiting. We had a budget. It was a generous budget. We never could not do anything because we didn't have funds. And there was no teaching you had to do except for the people in your lab. You could focus on what you wanted to do with any time and energy you wanted to put into it. It was an absolutely wonderful place for a young scientist to grow up. It was unmeasured. You can't describe how good it was.

GC: Okay. I'll stop the tape now. Thank you so much.

ES: You're welcome.

End of interview